



**Benefits of endocardial and multisite pacing are dependent on the type of left ventricular electric activation pattern and presence of ischemic heart disease: insights from electroanatomic mapping.**

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# Benefits of Endocardial and Multisite Pacing Are Dependent on the Type of Left Ventricular Electric Activation Pattern and Presence of Ischemic Heart Disease

## Insights from Electroanatomic Mapping

Matthew R. Ginks, MD; Anoop K. Shetty, MBBS; Pier D. Lambiase, PhD; Simon G. Duckett, MD; Julian Bostock, MSc; Janet L. Peacock, PhD; Kawal S. Rhode, PhD; Cliff Bucknall, MD; Jaswinder Gill, MD; Peter Taggart, MD; Christophe Leclercq, MD; Gerald S. Carr-White, PhD; Reza Razavi, MD; C. Aldo Rinaldi, MD

**Background**—There is considerable heterogeneity in the myocardial substrate of patients undergoing cardiac resynchronization therapy (CRT), in particular in the etiology of heart failure and in the location of conduction block within the heart. This may account for variability in response to CRT. New approaches, including endocardial and multisite left ventricular (LV) stimulation, may improve CRT response. We sought to evaluate these approaches using noncontact mapping to understand the underlying mechanisms.

**Methods and Results**—Ten patients (8 men and 2 women; mean [SD] age 63 [12] years; LV ejection fraction 246%; QRS duration 161 [24] ms) fulfilling conventional CRT criteria underwent an electrophysiological study, with assessment of acute hemodynamic response to conventional CRT as well as LV endocardial and multisite pacing. LV activation pattern was assessed using noncontact mapping. LV endocardial pacing gave a superior acute hemodynamic response compared with conventional CRT (26% versus 37% increase in LV  $dP/dt_{max}$ , respectively;  $P<0.0005$ ). There was a trend toward further incremental benefit from multisite LV stimulation, although this did not reach statistical significance ( $P=0.08$ ). The majority (71%) of patients with nonischemic heart failure etiology or functional block responded to conventional CRT, whereas those with myocardial scar or absence of functional block often required endocardial or multisite pacing to achieve CRT response.

**Conclusions**—Endocardial or multisite pacing may be required in certain subsets of patients undergoing CRT. Patients with ischemic cardiomyopathy and those with narrower QRS, in particular, may stand to benefit. (*Circ Arrhythm Electrophysiol.* 2012;5:889-897.)

**Key Words:** bundle branch block ■ cardiac resynchronization therapy ■ electrophysiology mapping ■ endocardium ■ hemodynamics

Cardiac resynchronization therapy (CRT) is an established treatment for selected patients with heart failure.<sup>1-4</sup> However, clinical response remains highly variable.<sup>5</sup> Even among patients with left bundle branch block (LBBB), there is heterogeneity in the location of conduction block and resulting left ventricular (LV) activation pattern.<sup>6,7</sup> Two broad patterns of LV activation have been described: type I activation, with slow propagation from the septum to lateral wall, and type II activation, with a U-shaped activation pattern resulting from a line of functional conduction block. A type II activation pattern would be expected to be more amenable to correction by LV stimulation, and indeed this pattern is associated with a favorable response to CRT.<sup>8</sup> Another key determinant of CRT response is the presence, location and burden of myocardial scar, and the position of the LV lead with respect to these regions.<sup>9-12</sup> Even in patients with nonischemic cardiomyopathy

(NICM), there may be significant variability in CRT response according to LV pacing site,<sup>13</sup> which may be because of the presence of zones of slow conduction.<sup>14</sup> Endocardial LV stimulation represents an alternative approach to avoid these areas without the constraints of the coronary venous anatomy and may be more effective than conventional epicardial CRT via the coronary sinus (CS).<sup>15</sup> Another strategy to improve CRT response is to position 2 LV leads to perform multisite LV pacing and simultaneously recruit a larger volume of myocardium. Conflicting results of the acute hemodynamic response (AHR) to dual-site pacing have been reported.<sup>16-18</sup>

### Clinical Perspective on p 897

We hypothesized that endocardial and multisite LV stimulation may be most beneficial in patients unlikely to benefit from standard CRT, including those with myocardial

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scar and a type I LV activation pattern. We set out to examine the underlying mechanisms whereby such novel pacing techniques may improve CRT response in relation to the underlying electric activation pattern and presence or absence of scar using noncontact mapping, cardiac magnetic resonance (CMR), and acute hemodynamic measurements.

## Methods

### Patients

St Thomas' Hospital Research Ethics Committee approved the study, and all patients provided written informed consent. Eligible patients were  $\geq 18$  years old and fulfilled conventional CRT criteria.<sup>19</sup> Patients with hemodynamically significant aortic valve disease, mechanical right heart valve or aortic valve, peripheral vascular disease, atrial arrhythmia, or contraindication to anticoagulation were excluded because they would not be able to undergo the protocol for the electrophysiology/noncontact mapping study (which was not part of routine CRT work-up). The study protocol was performed at least 1 week before standard CRT implantation. Patients with ischemic and NICM were studied, and the etiology of heart failure was confirmed on the basis of clinical history, 12-lead ECG, coronary angiogram, and CMR imaging.

### Cardiac Magnetic Resonance

CMR was used to quantify LV function and volumes. Late gadolinium enhancement CMR imaging was performed after the administration of a gadolinium-based contrast agent to assess myocardial scar or fibrosis. CMR was performed with a 1.5-T scanner (Philips Medical Systems), and late enhancement imaging was performed 15 to 20 minutes after the administration of 0.1 to 0.2 mmol/kg gadopentetate dimeglumine (Magnevist; Bayer Healthcare) using conventional inversion recovery techniques.<sup>20</sup>

### Electrophysiological Study

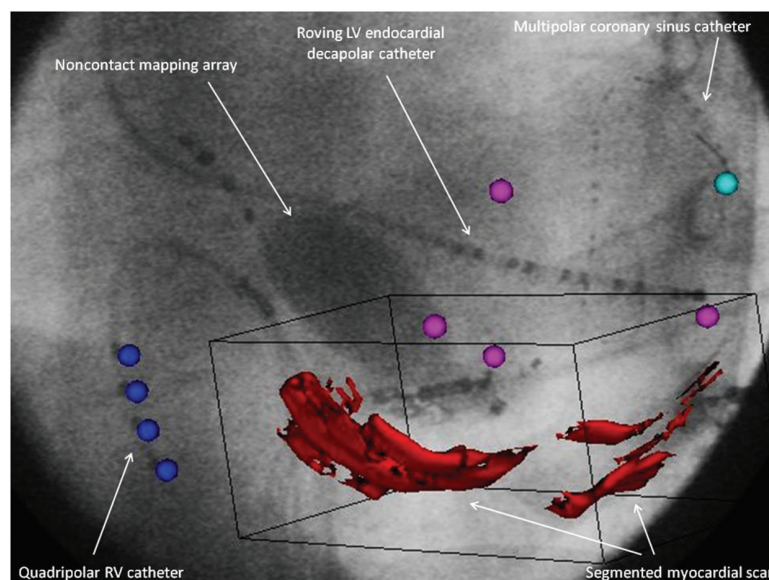
Procedures were performed in a hybrid x-ray/magnetic resonance imaging interventional cardiac catheter laboratory. Patients were sedated using diazepam (5–10 mg). Bilateral femoral venous access was used to place 5F Supreme quadripolar catheters (St. Jude Medical, St. Paul, MN) to the high right atrium, the bundle of His, and right ventricular apex to perform atrial and ventricular sensing and pacing. A 2.5F Pathfinder multipolar catheter (Cardima Inc, Fremont, CA) was introduced to the coronary sinus via an 8F SL3 sheath

(St. Jude Medical) and passed to a posterolateral or lateral branch of the CS to perform epicardial LV pacing to replicate standard CRT. A 9F EC1000 noncontact mapping array (St. Jude Medical) was passed via the femoral artery retrogradely across the aortic valve to the LV cavity. Through the other femoral artery, a 6F Livewire (St. Jude Medical) steerable decapolar catheter was passed to the LV cavity to reconstruct the chamber geometry, along with a Certus PressureWire (Radi Medical Systems, Uppsala, Sweden). This is a high fidelity wire, acquiring data at 400 Hz. Intravenous heparin (70 U/kg) was given to achieve systemic anticoagulation (target activated clotting time, 300–350 seconds). A left anterior oblique fluoroscopic view of the catheters in the heart at the time of the electrophysiological study is shown in Figure 1.

A pacing protocol was performed in a random fashion (100 beats per minute, atrioventricular delay 100 ms in all configurations, interventricular simultaneous): AAI (baseline), DDD right ventricle, and DDD BIV-CS (to reproduce conventional epicardial CRT via the posterolateral vein). LV endocardial pacing was performed: DDD LV endocardial (LV-EN) and DDD BIV endocardial (right ventricular and LV-EN: BIV-EN). In all modes involving LV endocardial pacing, we positioned the LV rove catheter in at least 3 different endocardial positions: anterior, lateral, and posterior. Capture was verified in VVI mode at each ventricular pacing site. To exclude fusion between intrinsic activation and LV pacing, both QRS morphology and the LV activation wave front on noncontact mapping were analyzed. Multisite LV pacing was performed (TRI-V), which was a combination of BIV-CS and LV-EN pacing, with simultaneous stimulation for all ventricular pacing sites. TRI-V stimulation was performed at each new LV-EN site.

### Noncontact Mapping

The EnSite 3000 system (St. Jude Medical), with the EC1000 multielectrode array mapping catheter, uses the inverse solution method to reconstruct endocardial unipolar potentials within the LV cavity. The accuracy of this technique has been validated previously.<sup>21</sup> Endocardial maps were obtained in sinus rhythm and in each pacing configuration. The virtual unipolar electrograms recorded from the endocardial surface were used to measure the LV activation time (LVAT). The electrograms were acquired at 1200 Hz, giving a temporal resolution of 0.83 ms. The high-pass filter was set at 8 Hz. The onset of activation was defined as the first peak negative dV/dt at any point in the left ventricle. The end of LV activation was defined as the time of the latest peak negative unipolar electrogram on the virtual endocardial surface. The activation pattern of the LV was determined on the basis of the presence or absence of lines of functional block.<sup>6</sup>



**Figure 1.** Left anterior oblique fluoroscopic image of noncontact mapping array and electrophysiological catheters in situ during a typical case. The color overlay shows left ventricular (LV) endocardial lead positions in magenta, right ventricular (RV) quadripolar electrodes in blue, tip of coronary sinus multipolar electrode in cyan, and scar segmented from cardiac magnetic resonance overlaid in red onto fluoroscopic image.



## Hemodynamic Assessment

Hemodynamic parameters were assessed at baseline (in AAI mode) and in each pacing mode once steady-state pacing had been achieved for a minimum of 1 minute. We used the pressure wire to derive real-time mean peak LV  $\text{dP/dt}_{\text{max}}$  as a marker of LV contractility, with 3 measurements in each pacing mode taken over a minimum of 10 seconds each. An increase in LV  $\text{dP/dt}_{\text{max}}$  of  $\geq 10\%$  from baseline AAI pacing was considered to represent positive AHR.<sup>22</sup>

## Statistical Analysis

Continuous variables are expressed as mean (SD). Data were analyzed using generalized estimating equations using an exchangeable correlation structure to explore the extent of differences between pacing methods. All pacing methods were compared with each other, and to avoid type 1 errors, *P* values were corrected using the Bonferroni adjustment. To perform a Bonferroni correction for each *P* value, the *P* value was divided by the number of comparisons made. For LV  $\text{dP/dt}_{\text{max}}$ , there were 5 comparisons between pacing modes; therefore,  $P < 0.01$  was considered significant at the 5% level.

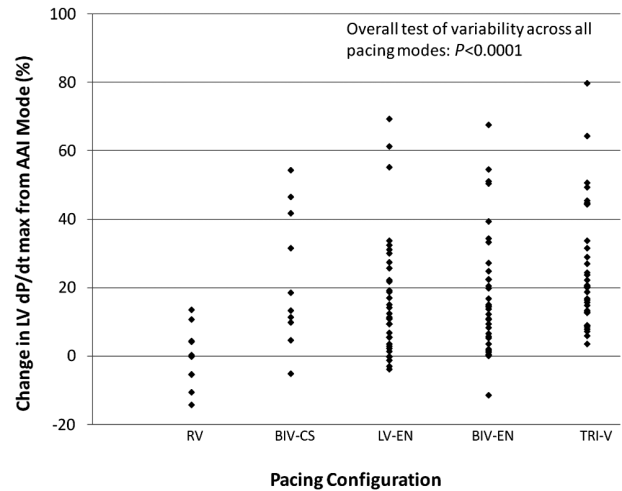
## Results

### Patient Demographics

Patient demographics are shown in Table 1. All patients had LBBB and were in New York Heart Association class III, despite optimal drug treatment. The invasive nature of the study (excluding patients with significant peripheral vascular disease) resulted in a predominance of patients with NICM.

### AHR to Pacing

Ten patients were studied. The mean AHR at the optimal pacing site is shown in Figure 2. In sinus rhythm, the mean (SD) LV  $\text{dP/dt}_{\text{max}}$  was 829 (161) mm Hg/s, increasing by 5% to 870 (201) mm Hg/s with AAI pacing, which was used as a baseline to assess other measurements to control for the effect of heart rate. There was no significant change from baseline with right ventricular endocardial pacing (861 [234] mm Hg/s). With BIV-CS pacing, there was a 26% increase from baseline to 1043 (378; 95% CI, 17.1–30.3) mm Hg/s. With LV-EN pacing, there was a greater increase from baseline of 37% to 1135 (412; 95% CI, 29.4–42.5) mm Hg/s, which was similar to BIV-EN pacing at 1114 (410; 95% CI, 29.3–42.4) mm Hg/s. The greatest AHR was seen with TRI-V pacing, with a 47% increase from baseline



**Figure 2.** Mean  $\text{dP/dt}_{\text{max}}$  for all pacing modalities in all 10 patients. This is displayed as the change in mean peak  $\text{dP/dt}_{\text{max}}$  resulting from pacing at the optimal site in each pacing configuration, compared with baseline (AAI pacing). LV indicates left ventricular; RV, right ventricular; BIV, biventricular; TRI-V, simultaneous BIV-CS and LV endocardial (EN).

to 1207 (464; 95% CI, 35.0–48.2) mm Hg/s. There was a statistically significant difference between right ventricular and all other pacing modes ( $P < 0.0001$ ) and a significant improvement compared with BIV-CS pacing with all LV-EN pacing configurations ( $P < 0.0005$ ). There was an improvement as a result of TRI-V pacing compared with other LV-EN pacing modes, which did not reach statistical significance ( $P = 0.08$ ).

### Effect of LV Pacing Site on AHR

The overall variability in hemodynamic response according to LV-EN pacing site (anterior versus posterior versus lateral) was not statistically significant ( $P = 0.073$ ). The mean difference in AHR between LV-EN and BIV-EN across pacing site was 0.93 (95% CI, -6.0 to 7.9), and the mean difference between LV-EN and TRI-V was 8.53 (95% CI, 1.56–15.51). The mean difference between the anterior and lateral pacing sites was 2.11 (95% CI, 5.52–9.73) and between the anterior and posterior sites was 3.00 (95% CI, -10.24 to 4.24).

### Effect of Heart Failure Etiology on AHR

Seven patients had NICM with no scar on late gadolinium enhancement CMR. Patients with NICM had a mean increase from baseline of 214 (224) mm Hg/s (26%) with BIV-CS pacing, 316 (254) mm Hg/s (37%) with LV-EN, 295 (245) mm Hg/s (36%) with BIV-EN, and 388 (304) mm Hg/s (47%) with TRI-V pacing. Five of the 7 (71%) patients with NICM were acute responders with standard BIV-CS pacing. Notably, the 2 patients with NICM who were nonresponders to BIV-CS pacing had a type I activation pattern, and both responded to endocardial and multisite (TRI-V) stimulation. Patients with ischemic cardiomyopathy (ICM) had a mean increase in LV  $\text{dP/dt}_{\text{max}}$  of 108 (74) mm Hg/s (12%) with standard CRT (BIV-CS pacing) compared with 249 (103) mm Hg/s (26%) with LV-EN, 312 (97) mm Hg/s (32%) with BIV-EN, and 391 (148)

**Table 1. Baseline Characteristics of the Study Population**

Parameter	Mean (SD) or Number
Age, y	63 (12)
Sex (M:F)	8:2
NYHA class III	10
MLWHFQ	45 (27)
Etiology (ischemic:nonischemic)	3:7
LVEF, %	24 (6)
QRS duration, ms	161 (24)
LVEDV, mL	273 (59)

NYHA indicates New York Heart Association; MLWHFQ, Minnesota Living With Heart Failure Questionnaire; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume (calculated using Simpson biplane method).

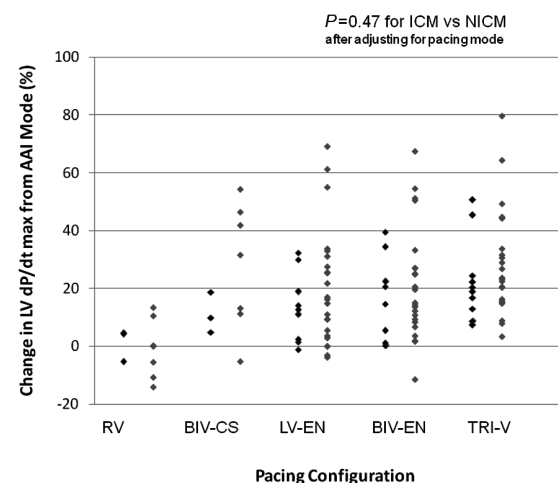
mm Hg/s (40%) with TRI-V pacing (Figure 3). After adjusting for the mode of pacing, the difference in AHR between ICM and NICM was not significant (mean difference,  $-7.82$ ; 95% CI,  $-28.93$  to  $13.28$ ;  $P=0.47$ ) (Figure 3 and Table 2).

### Stimulation in Ischemic Patients and Relationship to Scar

All the 3 patients with ICM exhibited late gadolinium enhancement on CMR. One patient with ICM had type I activation with a lateral line of block. With standard CS pacing, this patient was a nonresponder (5% increase in LV  $dp/dt_{max}$ ) but became an acute responder with endocardial pacing, with a response of 34% that increased to 45% with TRI-V stimulation. In this patient, the epicardial CS lead was overlying a region of scar/slow conduction defined by noncontact mapping/CMR. The second patient with ICM had a type I activation pattern and had an AHR of 19% with BIV-CS pacing but a more marked AHR of 39% with endocardial stimulation and a further rise to 51% with TRI-V pacing. In this patient, the CS lead was not located in an area of scar or slow conduction. The third patient with ICM exhibited type II activation and was a hemodynamic nonresponder with BIV-CS pacing (9%) but improved to 14% with endocardial and to 24% with TRI-V pacing. In this patient, the CS lead was not located in an area of scar or slow conduction. Thus, all patients with ICM had an incremental benefit with endocardial and TRI-V pacing, and 2 of 3 classified as nonresponders with standard BIV-CS pacing responded to endocardial or TRI-V pacing. In only 1 patient was the CS lead located in an area of scar/slow conduction. Figure 1 shows an example of a patient with ICM, with the location of the CS lead and endocardial pacing sites marked, as well as their relationships to a myocardial scar.

### Importance of Activation Pattern

Five patients had type I and 5 had type II activation on the basis of noncontact mapping (Figures 4 and 5). Patients with type I activation had a mean increase in LV  $dp/dt_{max}$  of 176



**Figure 3.** Acute hemodynamic response (percentage change in left ventricular [LV]  $dp/dt_{max}$  from AAI mode) in patients with ischemic cardiomyopathy (ICM) and nonischemic cardiomyopathy (NICM). RV indicates right ventricular; BIV, biventricular; TRI-V, simultaneous BIV-CS and LV endocardial (EN).

**Table 2.** Effect of Heart Failure Etiology and Activation Pattern on Acute Hemodynamic Response

Patient	Etiology	Scar	Activation Pattern	Responder BIV-CS	Responder Endocardial	Responder TRI-V
1	NICM	N	II	Y	Y	Y
2	NICM	N	II	Y	Y	Y
3	NICM	N	I	N	Y	Y
4	ICM	Y	I	N	Y	Y
5	NICM	N	II	Y	Y	Y
6	ICM	Y	I	Y	Y	Y
7	NICM	N	II	Y	Y	Y
8	NICM	N	I	N	Y	Y
9	ICM	Y	II	N	Y	Y
10	NICM	N	I	Y	Y	Y

TRI-V indicates simultaneous BIV-CS and LV endocardial; NICM, nonischemic cardiomyopathy; ICM, ischemic cardiomyopathy.

(277) mm Hg/s (15%) with BIV-CS pacing compared with 347 (284) mm Hg/s (33%) and 361 (276) mm Hg/s (35%) with LV-EN and BIV-EN, respectively, and 443 (327) mm Hg/s (43%) with TRI-V pacing. In patients with type II activation, there was a mean increase of 188 (82) mm Hg/s (28%) with BIV-CS pacing compared with 229 (120) mm Hg/s (35%) with LV-EN, 224 (87) mm Hg/s (33%) with BIV-EN, and 319 (180) mm Hg/s (45%) with TRI-V pacing. Of patients with a type I pattern, only 2 of 5 (40%) were classified as acute responders with standard BIV-CS pacing; however, 5 of 5 patients (100%) responded with endocardial or TRI-V pacing. Of the patients with type II activation, 4 of 5 (80%) were acute responders with BIV-CS pacing; the 1 nonresponder (ICM) responded with endocardial and TRI-V pacing. There was a lesser incremental benefit with endocardial or TRI-V pacing compared with BIV-CS pacing in patients with type II activation. After adjusting for the effect of pacing mode, patients with type I activation did not differ significantly in the degree of response from those with type II activation (mean difference, 1.39; 95% CI,  $-11.55$  to  $14.34$ ;  $P=0.83$ ; Figure 5).

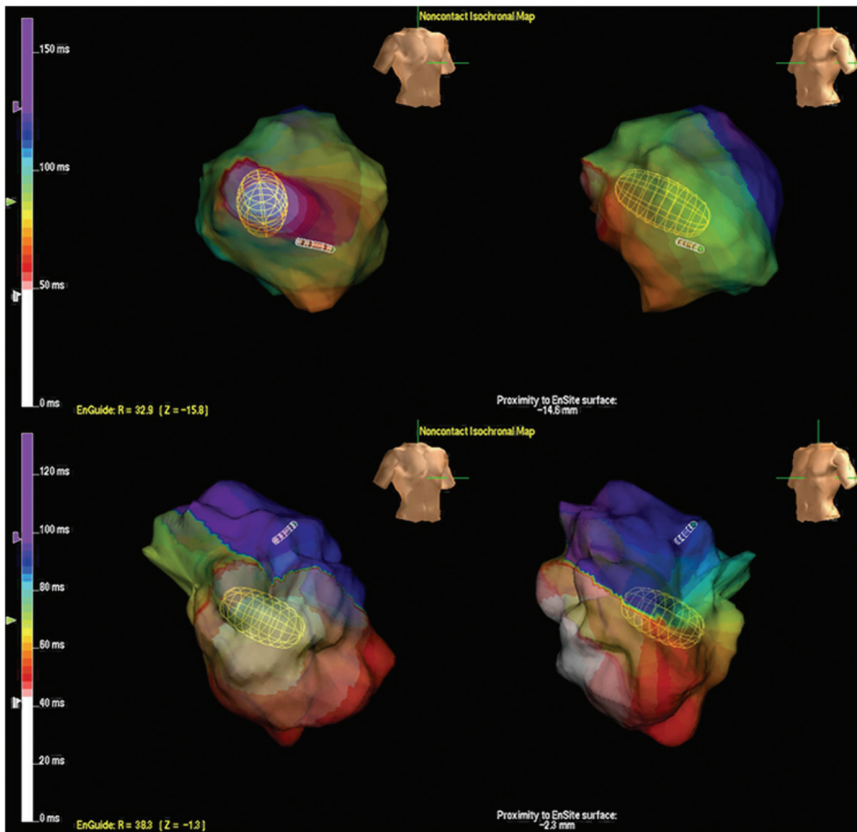
### Effect of Pacing on QRS Duration and LVAT

Results are shown in Figure 6 and Table 3. There was variation in QRS duration as a result of pacing mode ( $P<0.0001$ ), which was of borderline significance after adjusting for activation pattern, with a mean difference of 25.34 (95% CI,  $-0.35$  to  $51.04$ ;  $P=0.053$ ). In a similar way, LVAT also varied significantly overall ( $P=0.0003$ ), but the effect of the activation pattern was not significant (mean difference, 3.01; 95% CI,  $-10.45$  to  $16.46$ ;  $P=0.66$ ).

## Discussion

### LV Activation Pattern and Hemodynamic Response to Pacing

Our patients with LBBB and LV dysfunction exhibit varied hemodynamic responses to different pacing modalities, which were related to both the underlying etiology and the type of LV activation. Patients with ICM and type I activation

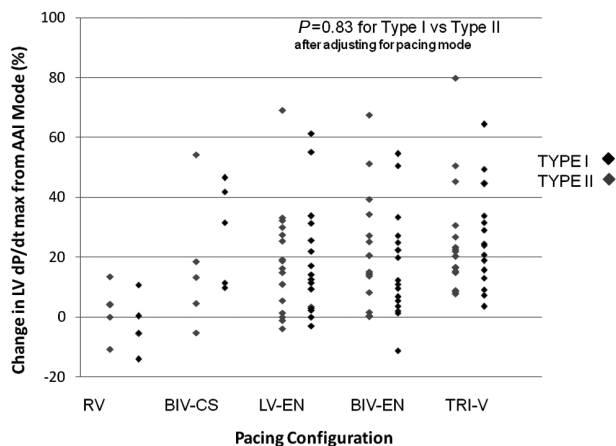


**Figure 4.** Activation patterns characterized by noncontact mapping. **Upper panel:** Type I activation pattern. The isochronal map shows a smooth propagation of the activation wave front from left ventricular (LV) septum to lateral wall. **Lower panel:** Type II activation pattern. The isochronal map shows a line of block in the anterior wall with the activation wave front passing around the inferior LV wall before it reaches the lateral wall.

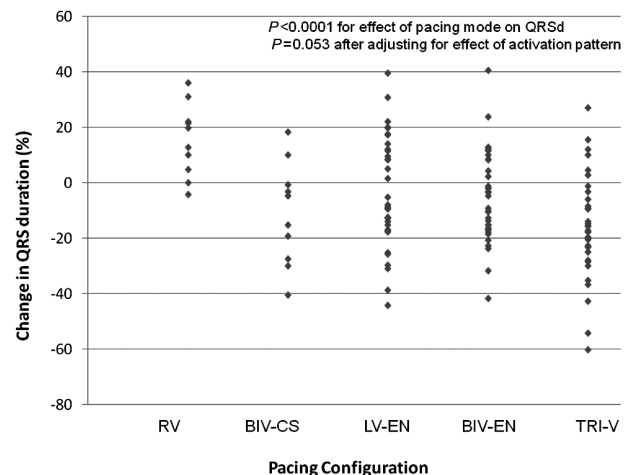
exhibited a lesser response to conventional CS-based CRT than patients with NICM and a type II activation pattern. However, this difference was not found to be statistically significant because the study was not powered to address this issue. Importantly, there were patients classified as hemodynamic nonresponders with standard CRT who responded to nonstandard forms of CRT (endocardial pacing and multisite LV stimulation). These patients tended to have ICM and a type I LV activation pattern, which are recognized markers of poor CRT response. In comparison, patients with NICM and a type II activation pattern typically identified as

responding well to standard CRT did not require alternative forms of non-CS-based pacing to derive AHR. Notably, the 2 patients with NICM who were nonresponders to CS pacing had a type I activation pattern.

Our patients with type II activation tended to have a broader QRS (174 versus 152 ms;  $P=0.09$ ) but similar LVAT (79 versus 82 ms). There was a good correlation between QRS duration and LVAT ( $r=0.64$ ) in patients with type I activation. This is intuitive because this group is thought to have relatively normal transseptal activation and slow homogeneous wave front propagation.<sup>6</sup> In contrast, there was a poor correlation



**Figure 5.** Hemodynamic response to pacing according to baseline left ventricular (LV) activation pattern. RV indicates right ventricular; BIV, biventricular; TRI-V, simultaneous BIV-CS and LV endocardial (EN).



**Figure 6.** QRS duration by pacing mode. RV indicates right ventricular; BIV, biventricular; TRI-V, simultaneous BIV-CS and LV endocardial (EN).

**Table 3. Effect of Pacing on QRS duration and LVAT**

Pacing Configuration		AAI	RV	BIV-CS	LV-EN	BIV-EN	TRI-V
QRS duration, ms							
	All	165 (23)	196 (33)	148 (20)	162 (37)	159 (30)	141 (30)
	Type I	152 (12)	178 (16)	160 (4)	152 (29)	159 (26)	146 (20)
Mean (SD)	Type II	174 (27)	208 (46)	134 (29)	161 (49)	155 (32)	129 (37)
LVAT, ms							
	All	81 (18)	85 (17)	78 (22)	91 (24)	83 (22)	79 (19)
	Type I	82 (20)	92 (8)	85 (25)	80 (5)	85 (4)	74 (17)
Mean (SD)	Type II	79 (20)	77 (21)	69 (23)	105 (32)	68 (17)	77 (22)

LVAT indicates left ventricular activation time; RV indicates right ventricular; BIV, biventricular; TRI-V, simultaneous BIV-CS and LV endocardial (EN).

between LVAT and QRS duration in patients with type II activation ( $r=0.17$ ), which is likely to reflect variation in the location and extent of functional conduction delay. One would, therefore, expect type II activation to be associated with a broader QRS complex and that this conduction delay may be more readily overcome by conventional CRT. In contrast, type I activation constitutes a substrate that is less readily improved by conventional CRT because propagation is homogeneously slow from the septum to the lateral wall without a line of functional conduction block.

## Comparison With Previous Studies

### LV Activation

Heterogeneous ventricular activation in patients with LBBB using noncontact mapping was previously described by Auricchio et al<sup>6</sup>. The majority of patients evaluated had a type II/U-shaped activation pattern resulting from a line of functional conduction block. In these patients, an anterior line of functional block was associated with longer QRS duration and was more readily overcome with pacing the lateral LV, keeping with the idea that this substrate is more readily treated with conventional CRT. This has been borne out in larger-scale studies, such as Multicenter Automatic Defibrillator Implantation Trial (MADIT)-CRT,<sup>23</sup> in which patients with QRS duration >150 ms derived a greater degree of clinical benefit.

Fung et al<sup>8</sup> also found that the majority (15/23) of their patients with LBBB had type II conduction, which was associated with a greater frequency of both clinical and echocardiographic response to CRT. The authors found that type I activation was more common in patients with an ischemic (63%) versus a nonischemic etiology (20%), and they hypothesized that areas of infarcted myocardium causing morphologically based fixed conduction block may explain why patients with ICM may require alternative approaches to the delivery of CRT.

### Importance of LV Pacing Site

We did not find statistically significant differences among anterior, lateral, and posterior pacing sites in biventricular pacing configurations. This is in keeping with the findings of the MADIT-CRT study, in which the degree of benefit from CRT was similar in patients with anterior, lateral, and posterior LV lead positions.<sup>24</sup>

### Endocardial and Multisite Pacing

The AHR to multisite LV pacing (in different branches of the CS) has been reported previously. Pappone et al<sup>16</sup> studied the AHR to dual-site pacing in 14 patients and demonstrated improvements in systolic function that were associated with a greater reduction in paced QRS duration. Padeletti<sup>17</sup> performed dual-site LV pacing in 12 patients and concluded that the addition of a second LV lead had no incremental benefit over standard CRT if the LV lead was optimally positioned and the atrioventricular and interventricular delays were optimized. In a study of 26 patients with atrial fibrillation who were implanted with a CRT device with 2 LV leads, the investigators of the Triple Resynchronization In Paced Heart Failure Patients (TRIP-HF) study demonstrated improvements in reverse LV remodeling resulting from dual-site LV pacing over single-site LV pacing in conjunction with CRT during the 9-month follow-up.<sup>25</sup> Furthermore, 4 of 10 patients in the TRIP-HF study who did not have reverse LV remodeling with single-site LV pacing responded with dual-site LV pacing.

Other investigators have shown endocardial pacing to be superior to epicardial CRT in patients with NICM<sup>13</sup> and ICM.<sup>15</sup> One key mechanism may be that this approach facilitates pacing outside areas of scar/slow conduction because greater area of the myocardium is accessible when lead delivery is not constrained by the coronary venous anatomy. In one of our ischemic patients, the CS lead was in an area of slow conduction, which may explain the beneficial response to endocardial or multisite pacing. However, in the other 2 ischemic patients, the CS lead was not in a region of slow conduction or scar. These findings, albeit from a small number of patients, suggest that the mechanism of benefit with TRI-V may be that the mode of stimulation influences LV mechanics and loading conditions, rather than simply overcoming the proximity of the leads in relation to scar.

In addition, there are other potential physiological benefits from endocardial pacing,<sup>26</sup> which, by engaging the subendocardial Purkinje network, reproduces the gradient of LV contraction in systole in an endocardial to epicardial direction.<sup>27</sup> This may result in more rapid myocardial recruitment, maximizing the contractile response of the viable recruited myocytes. Strik et al<sup>28</sup> have recently reported



in this journal the results of their work on endocardial LV pacing in a chronic canine heart failure model. The authors demonstrated improved hemodynamics as a result of LV endocardial pacing compared with conventional epicardial CRT, which could be explained by the shorter path length and more rapid conduction resulting from endocardial LV pacing. In keeping with our findings, the authors did not find a significant reduction in endocardial LVAT with endocardial pacing; however, total LVAT, as well as transmural LVAT, was reduced. Our results support the superiority of endocardial pacing over CS pacing in certain patients and suggest a possible synergistic effect of simultaneous endocardial and epicardial stimulation (TRI-V stimulation) over an endocardial site alone. This may be because of recruitment of a larger volume of myocardium and may also be explained on the basis of reducing the transmural conduction time. This would be expected to shorten the QRS duration while not greatly affecting the endocardial LVAT. Indeed, our results suggest a greater reduction in QRS duration between BIV-EN and TRI-V pacing compared with the difference in LVAT between BIV-EN and TRI-V, which may reflect the reduction in transmural conduction.

#### **Clinical Implications for CRT**

Identification of a U-shaped LV activation pattern may allow better selection of optimal lateral wall LV lead placement and when absent may indicate a subgroup that should be considered for initial multipolar or endocardial LV pacing. An LV activation pattern is not always apparent from the surface ECG. However it would seem that the broader the QRS, the more likely the activation pattern will respond favorably to conventional CRT. Noncontact mapping is a highly invasive tool that is impractical for widespread use to determine CRT response, and use of other technologies, such as body surface mapping, may hold some promise to define activation patterns.<sup>29</sup>

In this study, endocardial and multisite pacing were of benefit to patients with ICM and NICM. Intuitively, one might expect patients with ICM and scar to have more to gain with multisite stimulation because areas of block may be overcome with multiple stimulation sites. However, patients with NICM may also have areas of slow conduction or block, which may not be readily detected by current CMR techniques.<sup>30</sup> Derval et al<sup>13</sup> have shown that even in patients with NICM there is significant variability in hemodynamic response to CRT depending on the pacing site, which may be related to areas of slow conduction.

At present, there are several important limitations to the clinical use of endocardial LV pacing. First, the requirement for delivery of the endocardial LV lead poses technical challenges. There currently is no dedicated equipment for transseptal access using a superior approach, and transseptal puncture is almost universally performed with the femoral approach. If this approach is used, a second step is required to pass the lead across the interatrial septum, and several different strategies for this have been described.<sup>31–33</sup> The second issue is that an endocardial LV lead mandates formal

anticoagulation and is likely to increase the risk of thromboembolism. However, this risk is difficult to quantify because many patients who are considered eligible for endocardial LV stimulation are anticoagulated for another reason, most commonly coexistent atrial fibrillation or mechanical valve prosthesis. Third, there is potential for interference with mitral valve function as a result of crossing the valve apparatus with the LV lead, and there may be an associated risk of endocarditis. In the event of device infection and should lead extraction be required, it is likely to require a surgical approach.

#### **Study Limitations**

Noncontact mapping relies on unipolar signal detection and may not reliably distinguish between signals from the opposite site of the septum because they are sensitive and reflect electrograms from the entire wall. Noncontact mapping may also be less accurate in the enlarged left ventricle. Given the invasive and complex nature of these clinical measurements, we studied a small number of patients. There are definite trends; however, because of these small numbers it is not possible to determine whether these differences are clinically significant. In addition, this study is underpowered to address the effect of etiology and activation pattern on CRT response. Therefore, this work raises mechanistic insights, but larger studies are required to investigate these issues further. A factor that is difficult to control for in such a small mechanistic study is the volume of viable myocardium available for recruitment during pacing; this would require a large population and normalization of the hemodynamic response to the volume of viable myocardium available for resynchronization.

#### **Conclusions**

A greater proportion of patients in this study derived acute hemodynamic benefit in response to endocardial and multisite (TRI-V) pacing. These were patients with ischemic heart disease and a type I activation pattern and less marked QRS prolongation. The hemodynamic effect seemed to be dependent on the activation pattern but not absolutely on the LVAT, suggesting discordance between electric and mechanical resynchronization. The effect of TRI-V pacing seemed to be incremental to the effect of endocardial pacing alone. This study highlights subgroups of patients who may respond to endocardial or multisite pacing. A large-scale trial is warranted to evaluate the effects of LV endocardial and multisite pacing to establish whether such alternative approaches should be considered in patients who have not responded to CRT.

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### CLINICAL PERSPECTIVE

Response to cardiac resynchronization therapy (CRT) varies greatly among patients. Two key determinants of response are the heart failure substrate and the method of delivery of resynchronization. In this small mechanistic study, 10 patients with heart failure who were scheduled to undergo CRT were extensively investigated with cardiac magnetic resonance and noncontact mapping to identify areas of myocardial scar and to define the left ventricular (LV) activation pattern. A pacing protocol was performed to include conventional CRT delivered from a lateral or posterolateral branch of the coronary sinus, as well as endocardial LV pacing at several different sites and multisite pacing from endocardial and coronary sinus sites simultaneously. The authors found that response rates to CRT delivered in a tributary of the coronary sinus was high in patients with nonischemic cardiomyopathy and in those with functional conduction block in the LV myocardium. However, subjects with an ischemic heart failure etiology or slow homogeneous LV activation patterns frequently required other forms of LV stimulation, such as endocardial or multisite pacing, to derive hemodynamic benefit. Although this is a small study, it raises the possibility that these patients (who typically have lower response rates to CRT) may derive response to CRT only with such novel pacing strategies. If this is borne out by larger studies, noninvasive assessment to identify these patients may help to optimize patient selection and tailor therapy.